

## Gene Section

### Review

# SNCG (synuclein, gamma (breast cancer-specific protein 1))

Artur Czekierdowski, Sylwia Czekierdowska

Ist Department of Gynecologic Oncology and Gynecology, Medical University in Lublin, Poland (AC);  
Department of Clinical Immunology, Medical University in Lublin, Poland (SC)

Published in Atlas Database: June 2007

Online updated version: <http://AtlasGeneticsOncology.org/Genes/SNCGID42343ch10q23.html>  
DOI: 10.4267/2042/38465

This work is licensed under a Creative Commons Attribution-Non-commercial-No Derivative Works 2.0 France Licence.  
© 2008 *Atlas of Genetics and Cytogenetics in Oncology and Haematology*

## Identity

**Hugo:** SNCG

**Other names:** BCSG1 (Breast Cancer-Specific Gene-1 Protein); Gamma-synuclein; Persyn; PERSYN; PRSN; SR; Synoretin

**Location:** 10q23.2

**Note:** Synuclein-gamma is a member of the synuclein family of proteins which are believed to be involved in the pathogenesis of neurodegenerative diseases. High levels of SNCG have been identified in advanced breast carcinomas suggesting a correlation between overexpression of SNCG and breast tumor development.

## DNA/RNA

### Description

Human SNCG gene consists of five exons that span about 5 kbp. The intron 1 contains two closely located AP1 recognition sequences. Deletion of these motifs greatly diminished the SNCG promoter activity, suggesting that AP1 is an important transactivator for SNCG transcription. SNCG transcription is primarily controlled by regulatory sequences located in intron 1 and exon 1 but not in the 5' flanking region. Synuclein expression is regulated predominantly at the level of SNCG gene transcription and/or SNCG mRNA stability.

## Protein

### Description

Encoded by human SNCG Gene (Synuclein Family), the highly conserved 127-amino acid 13 kD cytoplasmic gamma-Synuclein is similar to the amyloid protein nonamyloid beta fragment and to alpha-

synuclein and beta-synuclein. The gamma-synuclein protein is the least conserved of the synuclein proteins. The human gamma-synuclein is 87.7% and 83.8% identical to the mouse and rat proteins, respectively, which are 4-amino acids shorter. As for the alpha- and beta-synuclein proteins, the region of highest homology is the amino-terminal region. The synuclein proteins contain several repeated domains that display variations of a KTKEGV consensus sequence. This motif, repeated six to seven times in the amino-terminal portion of the protein, is reminiscent of the alpha-helical domains of the apolipoproteins and suggests lipid binding properties. The very high conservation between species for a specific repeated domain of a particular protein suggests that the repeated domains have arisen from the duplication of a single domain within an ancestral synuclein gene. Later, this ancestral gene may have undergone successive duplications to give rise to the three synuclein genes in which the repeated domains may still be able to diverge. The third domain, however, remained absolutely identical, KTKEGV, in all genes throughout all species. The same type of domain is present in proteins of the rho family. However, as of today, the role of these domains remains unknown.

### Expression

Mammalian gamma-synuclein was first identified as the so-called Breast Cancer-Specific Gene 1 (BCSG1) in a high-throughput direct differential-cDNA-sequencing screen for markers of breast cancer. Northern blot analysis showed that the gene is principally expressed in the brain, particularly in the substantia nigra. The protein is expressed in the peripheral nervous system, mainly in primary sensory neurons, sympathetic neurons, and motor neurons. Synuclein gamma was also detected in ovarian tumors,

and in the olfactory epithelium. A sequence dubbed synoretin was independently isolated from ocular tissues in a screen for novel proteins regulating phototransduction and is now thought to represent the bovine ortholog of gamma-synuclein. SNCG is expressed in brain, heart, skeletal muscle, ovary, testis, colon, spleen, pancreas, kidney and lung.

### Localisation

The three human synuclein genes are expressed in the thalamus, the substantia nigra, the caudate nucleus, and the amygdala. Only gamma-synuclein appears strongly expressed in the subthalamic nucleus. Although gamma-synuclein is not present in senile plaques, Lewy bodies or neurofibrillary tangles, a high level of gamma-synuclein immunoreactivity is detectable in dot-like structures which are characteristic axonal lesions in the brains of patients with neurodegenerative diseases. SNCG mRNA and gamma-synuclein protein were also detected in unstimulated and phytohaemagglutinin (PHA)-stimulated cultured lymphocytes from peripheral blood of normal donors. It has been shown previously by in situ hybridization that SNCG/BCSG1 mRNA is not expressed in normal adult breast tissue, but high levels of this mRNA are present in advanced infiltrating breast tumours. In paraformaldehyde fixed cells, SNCG displayed punctuate cytoplasmic staining, a pattern that is usually associated with markers of the endoplasmic reticulum or vesicular structures. It was also found that gamma-synuclein was not co-localized with cytokeratin, actin or tubulin arrays in these cells.

### Function

The normal cellular function of gamma-synuclein is as yet unknown, but interestingly exogenous expression of the protein increases the invasive and metastatic potential of breast tumors. The highly conserved N-terminal region is known to be important for the lipid interactions of the synucleins and the highly acidic C-terminal region has been suggested to possess chaperone-like activity, to regulate the aggregation of synucleins and to mediate protein-protein interactions. It seems that gamma-synuclein plays a role in neurofilament network integrity and may modulate axonal architecture, also, it may increase the susceptibility of neurofilament-H to calcium-dependent proteases and may also modulate the keratin network in skin. Phosphorylation by GRK5 appears to occur on residues distinct from other kinase target residues. Synuclein gamma is likely involved in the pathogenesis of neurodegenerative diseases and SNCG is expressed at very high level in advanced infiltrating breast cancer. Sequence analysis suggests that the protein from tumour cells (BCSG1) is different from the protein expressed in the nervous system (cDNA clones 1 and 4C) and that coded by the genomic clone W6H. Substitution of two lysines by glutamates in BCSG1

changes the overall charge of the persyn molecule and disturbs EKTKEGV repeats that are highly conserved in the synuclein family. Such changes should have serious consequences for protein structure and function. The dual role of SNCG in neurodegeneration and malignancy could involve common mechanisms. Changes in organization of the cell cytoskeleton are among the most prominent characteristics of both processes. The involvement of gamma-synuclein in regulating neurofilament network integrity raises the possibility that it may also affect the intermediate filament network in malignant breast epithelial cells.

### Homology

There are currently almost 200 DNA and protein sequences in the sequence databases with high homology to the synuclein gene or protein. All synuclein sequences available to date from *Homo sapiens*, *Mus musculus*, and *Rattus norvegicus* can be assigned to three distinct protein groups: alpha beta and gamma-synuclein. Synuclein proteins have also been identified in other organisms: synelfin is the alpha-synuclein ortholog in *Serinus*, phosphoneuroprotein 14 (PNP14) is the beta-synuclein ortholog in *Bos taurus*, and the first synuclein protein described in *Torpedo californica* corresponds to the human gamma-synuclein. Interestingly, no homologous proteins have yet been identified in *Escherichia coli*, *Saccharomyces cerevisiae*, *Caenorhabditis elegans*, or *Drosophila melanogaster*. Each of the three family members is composed of an N-terminal lipid-binding domain, containing a series of 11-residue imperfect repeats, and an acidic C-terminal domain. Among the human family members, gamma-synuclein 50% identical and 74% homologous to alpha-synuclein and 47% identical and 66% homologous beta-synuclein. The highly conserved N-terminal region is known to be important for the lipid interactions of the synucleins and the highly acidic C-terminal region has been suggested to possess chaperone-like activity, to regulate the aggregation of synuclein and to mediate protein-protein interactions. The very high degree of conservation in the lipid-binding N-terminal domains of all three synucleins strongly suggests that both beta and gamma-synuclein like alpha-synuclein bind to lipid membranes and adopt a highly helical structure. Nevertheless, differences in the sequences of the three proteins in both their N-terminal and C-terminal domains must be responsible for those differences that do exist in their individual functions, as well as for their different roles in disease.

### Mutations

**Note:** No tumor-specific mutations of the SNCG gene were found in breast tumors and tumor cell lines, but two linked polymorphisms in the coding region were detected, both in mRNA and in exons III and IV of the gene from G243C and T377A. These results reflect the

absence of two G→A (and consequently Glu→Lys) in tumor cell lines, tumors and control tissues. The above mentioned two linked polymorphic sites discriminate two alleles of the human *persyn* gene. The frequencies of the two alleles were the same in genomes of breast cancer and normal cells (20% G243/T377 and 80% C243/A377). Both alleles are transcriptionally active and are expressed with similar efficiency in heterozygotes.

### Epigenetics

Sequence analysis identified a CpG island in exon 1 of SNCG that contains 15 CpG sites, covering the region -169 to +81, relative to the translation start codon. CpG sites within the CpG island and its vicinity were partially and heterogeneously methylated in SNCG-negative breast cancer cell lines but unmethylated in SNCG-positive cells. SNCG expression correlates with complete demethylation of the exon 1 region. Specific methylation at the CpG sites 2, 5, 7, and 10-15, was sufficient to block the expression of SNCG gene in breast cell culture. Genomic sequencing and methylation-specific PCR assays have shown that SNCG CpG island is fully methylated in normal tissues of liver, esophagus, prostate, cervix, stomach, colon, and lung, but only partially methylated in breast tissue. Tumors from these tissues contain completely demethylated SNCG. Universal loss of the epigenetic control of SNCG gene expression in tumors and further demonstrating that the demethylation of SNCG CpG island is primarily responsible for the aberrant expression of SNCG protein in cancerous tissues have suggested an important role of gamma-synuclein-related epigenetic events in various malignancies. Reactivation of SNCG gene expression by DNA demethylation is a common critical contributing factor to malignant progression of many solid tumors and its expression in primary carcinomas is an effective molecular indicator of distant metastasis.

### Implicated in

**Note:** The possible involvement of gamma-synuclein in tumorigenesis first came to light when a gene named BCSG1 (Breast Cancer-Specific Gene 1) was shown to be overexpressed in advanced infiltrating carcinoma of the breast. In fact, BCSG1 and gamma-synuclein appear to be the same protein. SNCG protein is highly expressed in diversified cancer types, including the female hormone-sensitive cervical and breast cancers, male hormone-sensitive prostate cancer, four cancer types of the digestive system, and lung cancer. These cancers are currently the leading cause of mortality in both men and women. How SNCG induces disease progression in different cancer types remains elusive. Oncogenic activation of gamma-synuclein contributes to the development of breast and ovarian cancer by promoting tumor cell survival under adverse conditions

and by providing resistance to certain chemotherapeutic drugs. Overexpression of gamma-synuclein leads to constitutive activation of extracellular signal-regulated protein kinases (ERK1 / ERK2) and down-regulation of c-Jun N-terminal kinase 1 (JNK1) in response to environmental stress signals. Cells expressing gamma-synuclein are significantly more resistant to the chemotherapeutic drugs paclitaxel and vinblastine as compared with the parental cells. Activation of JNK1 and its downstream caspase-3 by paclitaxel or vinblastine is significantly down-regulated in gamma-synuclein-expressing cells, indicating that the apoptosis pathway activated by vinblastine or paclitaxel is blocked by gamma-synuclein. In breast cancer cells, SNCG has been shown to act as a chaperon for estrogen receptor and stimulate estrogen receptor-α signaling pathway that leads to cell proliferation. On the other hand, the inhibitory effects of SNCG on mitotic checkpoint function are mediated through the mitotic checkpoint kinase BubR1 and are independent of the expression status of estrogen receptor-α. The inhibitory effects of SNCG on mitotic checkpoint can be overthrown by enforced overexpression of BubR1 in SNCG-expressing cells. SNCG intracellularly associates with BubR1 together. This observation suggests that SNCG expression compromises the mitotic checkpoint control by inhibition of the normal function of BubR1, thereby promoting genetic instability, a recognized and important contributing factor in tumorigenesis. Because all synucleins have chaperone-like activities, they may interact with different proteins in different cellular background. Identifications of specific cellular targets of SNCG in different tumor types will provide insight to delineate its oncogenic functions in human malignancies.

### Breast cancer

**Note:** Patients whose tumors expressed SNCG had a significantly shorter disease-free survival and overall survival. They also had a high probability of death when compared with those whose tumors did not express SNCG. Multivariate analysis demonstrated that SNCG is an independent predictive marker for recurrence and metastasis in breast cancer progression. SNCG is expected to be a useful marker for breast cancer progression and a potential target for breast cancer treatment. In one study it has been shown that responses of 12 breast cancer cell lines to paclitaxel-induced mitotic arrest and cytotoxicity highly correlated with SNCG expression status. SNCG-positive cells exhibited a significantly higher resistance to paclitaxel-induced mitotic arrest than SNCG-negative cells. Down-regulation of SNCG expression directly increased the effectiveness of anti-microtubule drug-induced cytotoxicity in breast cancer cells without altering cell responses to doxorubicin. These new findings suggest that SNCG expression in breast

carcinomas is probably a causal factor contributing to the poor patient response to paclitaxel treatment.

### Ovarian cancer

**Note:** Several studies indicated that SNCG expression was not detectable in normal ovarian epithelium but was highly expressed in the vast majority of advanced staged ovarian carcinomas. Eighty-seven percent of ovarian carcinomas were found to express at least 1 type of synuclein, and 42% expressed all 3 synucleins (alpha, beta, and gamma) simultaneously. Highly punctate gamma synuclein expression was also observed in 20% of preneoplastic lesions of the ovary, including epithelial inclusion cysts, hyperplastic epithelium, and papillary structures, suggesting that synuclein gamma up-regulation may occur early in the development of some ovarian tumors. Demethylation is an important event in abnormal synuclein-gamma expression. The methylation pattern in ovarian cancer cells is different from that in breast cancer cells. In one of the studies that examined SNCG-nonexpressing ovarian cancer cells, all of the CpG sites were completely methylated instead of selective methylation at certain sites shown in breast cancer cells, thereby suggesting a tissue-specific methylation pattern. Recent studies indicated that the detection of SNCG mRNA in tumor-positive tumors was strongly associated with demethylation or hypomethylation of SNCG gene. Methylation status was not correlated with FIGO stage or histological type of tumor. Tumor grading was strongly associated with methylation status but due to relatively small group of studied samples (43 cases) this observation requires further confirmation. Another interesting observation was that in 21% of samples both products of amplification were present and all these cases were SNCG mRNA-positive. This observation could suggest that partial methylation of SNCG probably does not influence on synuclein expression in ovarian cancer tissue. Comparison of the methylation status of SNCG and the expression of synuclein-gamma in breast and ovarian cancer cell lines in another study indicated a strong correlation between hypomethylation of the CpG island and SNCG expression in cancer cell lines. The methylation pattern in ovarian cancer cells was different from that in breast cancer cells. The analyzed CpG sites in ovarian cancer cells were all methylated in contrary to a selective methylation at certain sites shown in breast cancer cells, thereby suggesting a tissue-specific methylation pattern. Moreover, when exon 1 was partially and heterogeneously methylated, then SNCG expression in breast cancer cells was not detected.

### Lung cancer

**Note:** SNCG is not expressed in normal lung tissues, but it is highly expressed in lung tumors. It has been demonstrated that cigarette smoke extract (CSE) has strong inducing effects on SNCG gene expression in

lung cancer cells through demethylation of SNCG CpG island. CSE treatment also augments the invasive capacity of cells in an SNCG-dependent manner. These new findings demonstrate that tobacco exposure induces the abnormal expression of SNCG in lung cancer cells through downregulation of expression levels of DNA methyltransferases.

### Gastric cancer

**Note:** For the gastric cancer cell lines, SNCG mRNA expression strongly correlated with demethylation of SNCG exon 1 CpG islands. Whereas SNCG was not expressed in non-neoplastic gastric mucosal tissues obtained at autopsy, partial demethylation was present in these tissues. Demethylation occurs before malignant transformation and that only partial demethylation does not result in up-regulated SNCG mRNA expression. Thus, it appears that partial SNCG demethylation can occur in normal gastric mucosa, which then extends in some cases to become to fully demethylated, resulting in up-regulated SNCG mRNA expression.

## References

- Ji H, Liu YE, Jia T, Wang M, Liu J, Xiao G, Joseph BK, Rosen C, Shi YE. Identification of a breast cancer-specific gene, BCSG1, by direct differential cDNA sequencing. *Cancer Res* 1997;57:759-764.
- Lavedan C, Buchholtz S, Auburger G, Albin RL, Athanassiadou A, Blancato J, Burguera JA, Ferrell RE, Kostic V, Leroy E, Leube B, Mota-Vieira L, Papapetropoulos T, Pericak-Vance MA, Pinkus J, Scott WK, Ulm G, Vasconcelos J, Vilchez JJ, Nussbaum RL, Polymeropoulos MH. Absence of mutation in the beta- and gamma-synuclein genes in familial autosomal dominant Parkinson's disease. *DNA Research* 1998;5:401-402.
- Lavedan C, Leroy E, Dehejia A, Buchholtz S, Dutra A, Nussbaum RL, Polymeropoulos MH. Identification, localization and characterization of the human gamma-synuclein gene. *Hum. Genet* 1998;103:106-112.
- Ninkina NN, Alimova-Kost MV, Paterson JW, Delaney L, Cohen BB, Imreh S, Gnuchev NV, Davies AM, Buchman VL. Organization, expression and polymorphism of the human persyn gene. *Hum. Molec. Genet* 1998;7:1417-1424.
- Bruening W, Giasson BI, Klein-Szanto AJ, Lee VM, Trojanowski JQ, Godwin AK. Synucleins are expressed in the majority of breast and ovarian carcinomas and in preneoplastic lesions of the ovary. *Cancer* 2000;88:2154-2163.
- Lu A, Zhang F, Gupta A, Liu J. Blockade of AP1 transactivation abrogates the abnormal expression of breast cancer-specific gene 1 in breast cancer cells. *J Biol Chem* 2002;277:31364-31372.
- Pan ZZ, Bruening W, Giasson BI, Lee VM, Godwin AKJ. Gamma-synuclein promotes cancer cell survival and inhibits stress- and chemotherapy drug-induced apoptosis by modulating MAPK pathways. *Biol Chem* 2002;277:35050-35060.
- Gupta A, Godwin AK, Vanderveer L, Lu A, Liu J. Hypomethylation of the synuclein gamma gene CpG island promotes its aberrant expression in breast carcinoma and ovarian carcinoma. *Cancer Res* 2003;63:664-673.
- Gupta A, Inaba S, Wong OK, Fang G, Liu J. Breast cancer-specific gene 1 interacts with the mitotic checkpoint kinase BubR1. *Oncogene* 2003;22:7593-7599.

Wu K, Weng Z, Tao Q, Lin G, Wu X, Qian H, Zhang Y, Ding X, Jiang Y, Shi YE. Stage-specific expression of breast cancer-specific gene gamma-synuclein. *Cancer Epidemiol Biomarkers Prev* 2003;12:920-925.

Jiang Y, Liu YE, Goldberg ID, Shi YE. Gamma synuclein, a novel heat-shock protein-associated chaperone, stimulates ligand-dependent estrogen receptor alpha signaling and mammary tumorigenesis. *Cancer Res* 2004;64:4539-4546.

Yanagawa N, Tamura G, Honda T, Endoh M, Nishizuka S, Motoyama T. Demethylation of the synuclein gamma gene CpG island in primary gastric cancers and gastric cancer cell lines. *Clin Cancer Res* 2004;10:2447-2451.

Inaba S, Li C, Shi YE, Song DQ, Jiang JD, Liu J. Synuclein gamma inhibits the mitotic checkpoint function and promotes chromosomal instability of breast cancer cells. *Breast Cancer Res Treat* 2005;94:25-35.

Liu H, Liu W, Wu Y, Zhou Y, Xue R, Luo C, Wang L, Zhao W, Jiang JD, Liu J. Loss of epigenetic control of synuclein-gamma gene as a molecular indicator of metastasis in a wide range of human cancers. *Cancer Res* 2005;65:7635-7643.

Czekierdowski A, Czekierdowska S, Wielgos M, Smolen A, Kaminski P, Kotarski J. The role of CpG islands hypomethylation and abnormal expression of neuronal protein synuclein-gamma (SNCG) in ovarian cancer. *Neuro Endocrinol Lett* 2006;27:381-386.

Sung YH, Eliezer D. Secondary structure and dynamics of micelle bound beta- and gamma-synuclein. *Protein Sci* 2006;15:1162-1174.

Zhao W, Liu H, Liu W, Wu Y, Chen W, Jiang B, Zhou Y, Xue R, Luo C, Wang L, Jiang JD, Liu J. Abnormal activation of the synuclein-gamma gene in hepatocellular carcinomas by epigenetic alteration. *Int J Oncol* 2006;28:1081-1088.

Guo J, Shou C, Meng L, Jiang B, Dong B, Yao L, Xie Y, Zhang J, Chen Y, Budman DR, Shi YE. Neuronal protein synuclein gamma predicts poor clinical outcome in breast cancer. *Int J Cancer* 2007;(Epub ahead of print).

Liu H, Zhou Y, Boggs SE, Belinsky SA, Liu J. Cigarette smoke induces demethylation of prometastatic oncogene synuclein-gamma in lung cancer cells by downregulation of DNMT3B. *Oncogene* 2007 Mar 19;(Epub ahead of print).

Wu K, Quan Z, Weng Z, Li F, Zhang Y, Yao X, Chen Y, Budman D, Goldberg ID, Shi YE. Expression of neuronal protein synuclein gamma gene as a novel marker for breast cancer prognosis. *Breast Cancer Res Treat* 2007;101:259-67.

---

*This article should be referenced as such:*

Czekierdowski A, Czekierdowska S. SNCG (synuclein, gamma (breast cancer-specific protein 1)). *Atlas Genet Cytogenet Oncol Haematol.*2008;12(1):12-16.

---